Targeting Bcl-2 protein in treatment of melanoma still requires further clarifications

Expression of Bcl-2 protein has been demonstrated to reduce the apoptotic response to cytotoxic chemotherapy, and induction of apoptosis may become one of the main molecular targets in the treatment of melanoma (which indeed presents a well-recognized high resistance to conventional anticancer therapies) [1]. In recent past years, addition of oblimersen (G3139; Genta International Inc., NJ), an antisense oligonucleotide downregulating Bcl-2 expression, to a dacarbazine-based chemotherapy for the treatment of advanced melanoma has increased tumor-cell apoptosis in a phase I–II study [2] and improved overall survival in patients with normal serum lactate dehydrogenase in a randomized phase III clinical trial [3]. However, questions arise over the cause–effect relationship between the antiproliferative activity of oblimersen and somatic expression levels of the Bcl-2 protein.

On this regard, our preliminary evidence indicated that the effect of oblimersen on proliferation of melanoma cells seems to be independent on Bcl-2 expression. In particular, several melanoma cell lines established as short term cultures from primary tumors of melanoma patients (after obtaining their informed consent) were treated with oblimersen and the
cytotoxic response, in terms of cell growth reduction, was investigated. In our experience, the poorest antiproliferative activity of oblimersen was surprisingly detected in melanoma cell lines with the highest Bcl-2 expression levels; conversely, inhibition of cell growth was observed in cultured melanomas which did not express any detectable level of the Bcl-2 protein (Figure 1). Putting together ours with the published findings [2, 3], one could speculate that oblimersen, despite its putative high specificit (it is a phosphorothioate oligonucleotide recognizing the initiation codon region of the Bcl-2 mRNA), may induce a Bcl-2-independent cellular apoptosis and, thus, target different molecular pathways.

Analogously, majority of the recently developed tyrosine-kinase inhibitors, which were firstly isolated as active on specific molecular effectors, indeed target several types of cancer cell receptors and inhibit multiple molecular mechanisms [4]. Nevertheless, resistance to apoptosis through the Bcl-2 pathway is yet to be clarified and defective apoptotic response to anticancer agents may be caused by mechanisms other than Bcl-2 expression (silencing of Bcl-2 gene by highly specific interfering RNA has been demonstrated to fail in increasing the sensitiveness to a variety of cytotoxic agents in melanoma cells [5]).

In the light of recent advances, it appears evident that targeting a single component within the multiple signaling pathways involved in development and progression of human cancers is unlikely to yield significant antitumor responses. Therefore, further clarification of the main mechanisms implicated into the control of the apoptotic machinery (i.e., activation of other effectors of the apoptosis cascade and/or release of mitochondrial apoptogenic proteins) could permit to select the subsets of patients who would be expected to be more likely to respond to the anti-Bcl-2 treatment. More in general, making correlations between functionally associated molecular signatures and clinical response to therapy may avoid that targeted treatments in patients carrying one specific molecular alteration achieve different clinical outcomes due to the coexistence of additional alterations in alternative pathways. For sure, the introduction of targeted therapies is generating more questions than answers.

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Figure 1. Effect of oblimersen on growth of human melanoma cell lines. (A) Seven melanoma cell lines were cultured in presence of RPMI medium alone (negative control), 250 µM of oblimersen, and 10 µM etoposide (cytotoxic agent as positive control) for 6 days; cell proliferation was estimated by a standardized colorimetric assay. Results represent the average of triplicate cultures performed twice. (B) Representative western blot analysis showing different levels of Bcl-2 expression in the same series of melanoma cell lines.